HFD-60

NDA 18-074/S-028

NOV 13 1998

Eon Labs
Attention: Mary Mulligan
Regulatory Affairs Associate
227-l 5 North Conduit Ave.
Laurelton, NY 11413

Dear Ms. Mulligan:

Please refer to your supplemental new drug application dated August 3 1, 1998, received September 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Phendimetrazine Tartrate Sustained Release Capsules, 105 mg.

We note that this supplement was submitted as a "Special Supplement - Changes Being Effected" under 2 1 CFR 314.70(c).

This supplemental new drug application provides for changes to the CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE and OVERDOSAGE sections. Your submission does not state the date for implementing for the change.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted August 31, 1998). Accordingly, the supplemental application is approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

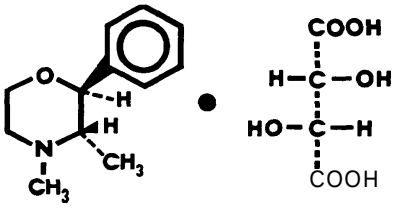
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Maureen Hess, MPH, RD, Consumer Safety Officer, at (301) 827-6411.

DESCRIPTION:

Phendimetrazine tartrate, as the dextro isomer, has the chemical name of (2S,3S)-3,4-dimethyl-2-phenylmorpholine L-(+)tartrate (1:1).

The structural formula is as follows:



$C_{12}H_{17}NO.C_4H_6O_6$ M.W. 341.36

Phendimetrazine tartrate is a white, odorless crystalline powder.

It is freely soluble in water; sparingly soluble in warm alcohol, insoluble in chloroform, acetone, ether and benzene.

Each capsule, for oral administration, contains 105 mg Phendimetrazine Tartrate manufactured in a special base designed for prolonged release. Inactive ingredients: FD&C Blue No. 1, FD&C Red No. 40, gelatin, pharmaceutical glaze, povidone, silicon dioxide, sodium lauryl sulfate, corn starch, sucrose, and talc.

CLINICAL PHARMACOLOGY:

Phendimetrazine tartrate is a phenylalkylamine sympathomimetic amine with pharmacological activity similar to the prototype drugs of this class used in obesity, the amphetamines. Actions include central nervous system stimulation and elevation of blood pressure. Tachyphylaxis and tolerance have been demonstrated with all drugs of this class in which these phenomena have been looked for.

Drugs of this class used in obesity are commonly known as "anorectics" or "anorexigenics". It has not been established, however, that the action of such drugs in treating obesity is primarily one of appetite suppression. Other central nervous system actions or metabolic effects, may be involved, for example.

Adult obese subjects instructed in dietary management and treated with anorectic drugs, lose more weight on the average than those treated with placebo and diet, as determined in relatively short term clinical trials.

The magnitude of increased weight loss of drug-treated patients over placebo-treated patients is only a fraction of a pound a week. The rate of weight loss is greatest in the first weeks of therapy for both drug and placebo subjects and tends to decrease in succeeding weeks. The possible origins of the increased weight loss due to the various drug effects are not established. The amount of weight loss associated with the use of an anorectic drug vanes from trial to trial, and the increased weight loss appears to be related in part to variables other than the drug prescribed, such as the physician investigator, the population treated, and the diet prescribed. Studies do not permit conclusions as to the relative importance of the drug and non-drug factors on weight loss.

The natural history of obesity is measured in years, whereas the studies cited are restricted to a few weeks duration, thus, the total impact of drug-induced weight loss over that of diet alone must be considered clinically limited.

The active drug, 105 mg of Phendimetrazine Tartrate in each capsule of this special extended-release dosage form approximates the action of three 35 mg immediate release doses taken at four hour intervals.

The major route of elimination is via the kidneys where most of the drug and metabolites are excreted. Some of the drug is metabolized to Phenmetrazine and also Phendimetrazine-N-oxide.

The average half-life of elimination when studied under controlled conditions is about 3.7 hours for both the extended-release and immediate release forms. The absorption half-life of the drug from the immediate release 35 mg phendimetrazine tablets is appreciably more rapid than the absorption rate of the drug from the extended-release formulation.

INDICATIONS AND USAGE:

Phendimetrazine tartrate extended-release capsules are indicated in the management of exogenous obesity as a short term adjunct (a few weeks) in a regimen of weight reduction based on caloric restriction. The limited usefulness of agents of this class (see CLINICAL PHARMACOLOGY) should be measured against possible risk factors inherent in their use such as those described below.

CONTRAINDICATIONS:

Known hypersensitivity or idiosyncratic reactions to sympathomimetics.

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate and severe hypertension, hyperthyroidism and glaucoma. Highly nervous or agitated patients. Patients with a history of drug abuse. Patients taking other CNS stimulants, including monoamine oxidase inhibitors.

WARNINGS:

Tolerance to the anorectic effect of phendimetrazine develops within a few weeks. When this occurs, its use should be discontinued; the maximum recommended dose should not be exceeded.

Use of phendimetrazine tartrate within 14 days following the administration of monoamine oxidase inhibitors may result in a hypertensive crisis.

Abrupt cessation of administration following prolonged high dosage results in extreme fatigue and depression. Because of the effect on the central nervous system, phendimetrazine may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

PRECAUTIONS:

Caution is to be exercised in prescribing phendimetrazine tartrate for patients with even mild hypertension.

Insulin requirements in diabetes mellitus may be altered in association with the use of phendimetrazine and the concomitant dietary regimen.

Phendimetrazine may decrease the hypotensive effect of guanethidine.

The least amount feasible should be prescribed or dispensed at one timeinorder to minimize the possibility of overdosage.

Carcinogenesis, Mutagenesis, Impairment of Fertility Studies with Phendimetrazine Tartrate sustained release have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Phendimetrazine Tartrate sustained release. It is also not known whether Phendimetrazine Tartrate sustained release can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Phendimetrazine Tartrate sustained release should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Phendimetrazine Tartrate sustained release capsules are administered to a nursing mother.

Usage in Pregnancy: Safe use in pregnancy has not been established. Until more information is available, phendimetrazine tartrate should not be taken by women who are or may become pregnant unless, in the opinion of the physician, the potential benefits outweigh the possible hazards.

Usage in Children: Phendimetrazine tartrate is not recommended for use in children under 12 years of age.

ADVERSE REACTIONS,

Cardiovascular: Palpitation, tachycardia, elevated blood pressure.

Central Nervous System: Overstimulation, restlessness, insomnia, agitation, flushing, tremor, sweating, dizziness, headache, psychotic state, blurring of vision.

Gastrointestinal: Dryness of the mouth, nausea, diarrhea, constipation, stomach pain.

Genitourinary: Urinary frequency, dysuria, changes in libido.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: Phendimetrazine tartrate extended-release capsules are defined by the Drug Enforcement Administration as a Schedule III controlled substance.

Dependence: Phendimetrazine tartrate is related chemically and pharmacologically to the amphetamines. Amphetamines and related stimulant drugs have been extensively abused, and the possibility of abuse of phendimetrazine should be kept in mind when evaluating the desirability of including a drug as part of a weigh' reduction program. Abuse of amphetamines and related drugs may be associated with intense psychological dependence and severe social dysfunction. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with anorectic drugs include severe dermatoses, marked insomnia, irritability, hyperactivity and personality changes. The most severe manifestation of chronic intoxications is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE:

Acute overdosage with phendimetrazine tartrate may manifest itself by the following signs and symptoms: unusual restlessness, confusion, belligerence, hallucinations, and panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension, or hypotension and circulatory collapse. Gastro-intestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Poisoning may result in convulsions, coma, and death.

The management of overdosage is largely symptomatic. It includes sedation with a barbiturate. If hypertension is marked, the use of a nitrate or rapid-acting alpha receptor-blocking agent should be considered. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations for its use.

DOSAGE AND ADMINISTRATION,

Extended-release capsule: Since the product is an extended-release dosage form, limit to one extended-release capsule (105 mg Phendimetrazine Tartrate) in the morning (30-60 minutes before morning meal).

Each extended-release capsule contains 105 mg phendimetrazine tartrate in a Brown/Clear #1 capsule imprinted RPC 62.

Packed in bottles of 100,250,500, and 1000 capsules.

Store at controlled room temperature 15"- 30°C (59'-86"F).

DISPENSE IN A TIGHT CONTAINER AS DEFINED IN THE USP.

Rx only

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Rev. 4/98/
MF2056REV0498
Flat